Pulmonary Thrombosis with Transient Antiphospholipid Syndrome after Mononucleosis-like Illness

Kiminobu Tanizawa¹, Daisuke Nakatsuka², Eisaku Tanaka¹, Tetsuro Inoue¹, Minoru Sakuramoto¹, Masayoshi Minakuchi¹, Seishu Hashimoto¹, Satoshi Noma³, Teruhisa Azuma², Hiroyasu Ishimaru², Kazuhiro Hatta², Yoshiaki Kohri² and Yoshio Taguchi¹

Abstract

Antiphospholipid antibodies (aPL) have been reported to occur in numerous viral infections. We report a 24-year-old Japanese woman, who developed multiple venous thrombosis associated with the elevation of antinuclear antibody IgM after acute viral infection presenting a mononucleosis-like illness. Two months later, aPL and thromboses disappeared. In this case both parvovirus B19 and cytomegalovirus antibodies IgM were elevated, which indicated the possibility of cross-reaction.

Key words: pulmonary thrombosis, antiphospholipid syndrome, mononucleosis-like illness, parvovirus B19, cytomegalovirus

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Introduction

Antiphospholipid syndrome (APS) represents arterial or venous thrombosis associated with the presence of antiphospholipid antibodies (aPL). While APS is commonly associated with autoimmune disorders, transient aPL are often produced in response to viral infections (1). Human parvovirus B19 causes various clinical symptoms mimicking autoimmune disorders, including transient APS with venous thrombosis (2-6). Cytomegalovirus (CMV) also causes venous thrombosis in immunocompetent as well as immunosuppressed patients (7-13). We report a case of transient APS with multiple venous thrombosis after acute viral infection. Serological studies showed both possibilities of parvovirus B19 and CMV infection.

Case Report

A 24-year-old previously healthy woman was admitted with a 2-week history of fever and liver dysfunction. Physical examination demonstrated a fever of 38.9°C. She had no

conjunctival or pharyngeal injection. There was no hepatomegaly, splenomegaly or lymphadenopathy, and no skin eruption or joint abnormalities were noted. On admission laboratory studies demonstrated leukocytosis with atypical lymphocytes and elevation of CRP, LDH, AST and ALT. Biliary enzymes were normal. She was diagnosed as having infectious mononucleosis. Five days later, fever gradually resolved and laboratory tests showed improvement with supportive therapy. On the 8th hospital day, she developed an abrupt pain involving the right lateral chest and abdomen that was aggravated by deep breathing. On examination, her body temperature was 38.9°C, respirations 12 per minute and oxygen saturation was 98% while breathing ambient air. Auscultation of the chest and heart did not detect any abnormalities, but she had reported tenderness in the right lateral chest and abdomen. The next day, laboratory studies showed elevated TAT of 7.7 ng/mL, FDP of 44 µg/mL and FDP D-dimer of 29.8 µg/mL. There were no atypical lymphocytes and arterial gas analysis was normal. Chest radiography, electrocardiography and echocardiogram did not reveal any abnormalities. Enhanced computed tomography (CT) of the chest and abdomen showed subpleural consolidation in the

¹Department of Respiratory Medicine, Tenri Hospital, Nara, ²Department of General Internal Medicine, Tenri Hospital, Nara and ³Department of Radiology, Tenri Hospital, Nara

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Correspondence to Dr. Kiminobu Tanizawa, tanizawa@kuhp.kyoto-u.ac.jp

Figure 1. Multiple venous thrombosis. a: Consolidation in the right lower lung due to pulmonary infarction. b: Pulmonary arterial thrombosis in the right descending branch (arrowhead). c: Superior mesenteric venous thrombosis (arrowhead)

right S¹⁰, right pulmonary arterial and superior mesenteric venous thromboses (Fig. 1). Additional studies disclosed elevated titers of anticardiolipin (aCL) IgM antibody (13 MPL) and normal titers of anticardiolipin IgG antibody, lupus anticoagulant (the dilute Russell viper venom time: dRVVT) and anticardiolipin β 2glycoprotein- β (β 2GP- β) antibody. The patient also demonstrated antinuclear antibodies and antibodies to RNP, Scl-70 and Jo-1; other autoantibodies were negative. Complement was not decreased and biological test for syphilis was negative. Antithrombin-III, protein C and protein S were normal. Serological tests demonstrated positive IgM antibodies for both parvovirus B19 and CMV, but antibodies for Epstein-Barr virus, hepatitis A, C, HIV and HTLV-I were negative. There was neither CMV nor hepatitis B antigenemia. Magnetic resonance imaging (MRI) of the brain was normal and there was no deep venous thrombosis. She received anticoagulation therapy with heparin for one week, and the multiple thrombosis resolved completely. Two months later, aPL disappeared. Five months later, IgM antibodies for both parvovirus B19 and CMV returned to normal, indicating acute infection with these viruses. We continued anticoagulation therapy for 6 months and there has not been any recurrence of venous thrombosis.

Discussion

The transient presence of aPL after common viral infec-

tions is prevalent but not pathogenic in most cases (1). To our knowledge, there are only 2 reported cases of thrombotic events after acute infection of parvovirus B19 and 21 cases after CMV in immunocompetent adults (5-13). Reitblat et al described a healthy young man with acute parvovirus B19 infection who developed splenic infarction associated with elevation of aCL IgM and IgG (5). Asano et al reported the case of a healthy woman with acute parvovirus B19 infection who developed asymptomatic multiple pulmonary emboli associated with elevation of aCL IgM and lupus anticoagulant (6). In both cases, thrombosis and aPL disappeared or decreased within two months. Twenty-one cases of acute CMV infection included 6 cases of pulmonary emboli and 10 cases of portal vein thrombosis (7-13).

In the present case, both parvovirus B19 and CMV antibodies IgM were elevated. We suppose that this was due to either cross-reaction or coinfection. Cross-reaction has been reported between the commercial parvovirus B19 and CMV antibodies IgM: 20% of CMV IgM positive serum was positive for parvovirus B19 IgM; 8% of parvovirus B19 IgM positive serum was positive for CMV IgM (14). Both viruses cause mononucleosis-like illnesses and the transient presence of various autoantibodies (2, 3, 4, 11). The clinical course, including the transient presence of various autoantibodies, could not determine the pathogenic virus in this case.

In parvovirus B19 infection, aPL have been thought to be associated with thromboembolic events. In all three reported

cases including the present case, thromboembolic events were accompanied with the transient presence of aPL (5, 6). Landenberg et al reported that 58% of IgG aPL-positive children and 83% of those adults with rheumatic diseases showed acute or persistent infection of parvovirus B19. Based on these data, they concluded that parvovirus B19 was associated with the induction of aPL (15).

Molecular mimicry has been proposed as the main mechanism for production of aPL in parvovirus B19 infection (4-6). The parvovirus B19 particle consists of two structural proteins, VP1 and VP2. These proteins are identical except for the VP1-unique region at the amino-terminal of the VP1 protein (3). Lunardi et al reported that the synthesized VP1-specific IgG reacts specifically with human keratin, collagen type II, single-stranded DNA and cardiolipin (16). Landenberg et al reported that the phospholipase-A2-like activity is observed in the VP1-unique region of parvovirus B19 particle (15). This enzyme activity may lead to the generation of unnatural complexes with cellular proteins or unusual cleavage products from cellular phospholipids compounds that may induce aPL (15). In addition, the parvovirus B19 NS1 protein is also known to induce autoimmune phenomena by transactivation of the expression of TNF- α and IL-6 (17, 18).

In CMV infection, several mechanisms responsible for thromboembolic events have been proposed. Gharavi et al showed that aPL, that were induced in mice by immuniza-

tion with a CMV-derived peptide, caused thrombosis and activation of endothelial cells in vivo (19). However, in only 4 of 21 reported cases, aPL were positive (7-13). Other mechanisms, including endothelial damage due to direct infection or indirect inflammatory response, vascular cell activation and enhanced factor VIII synthesis or secretion have been speculated. In some cases, other predisposing factors for thrombosis were found: factor V Leiden mutation, use of contraceptive pills and prolonged rest (8, 9, 13).

The reason why aPL following viral infection are not pathogenic in most cases remains to be determined. One reason postulated is that most viral infections produce β 2-GPI-independent aPL (1, 6). β 2-GPI is a single chain normal plasma protein that binds anionic phospholipids as a co-factor and is considered to be a regulator of coagulation. Pathogenic aPL are thought to require β 2-GPI for binding to phospholipids (20). Gharavi et al showed that CMV infection can produce pathogenic aPL through the mechanism of molecular mimicry in mice (19). Loizou et al showed aPL produced in acute Parvovirus B19 infection demonstrated increased activities in the presence of β 2GPI unlike those from patients with other viral infections or syphilis (21). Another speculated reason is that aPL associated with viral infections usually persist for only a short period.

In conclusion, thromboembolic events can be followed by the transient induction of aPL after acute viral infection presenting a mononucleosis-like illness.

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